Roman Hajek

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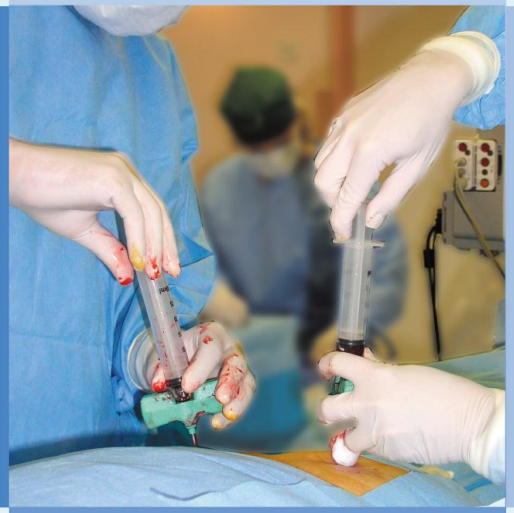
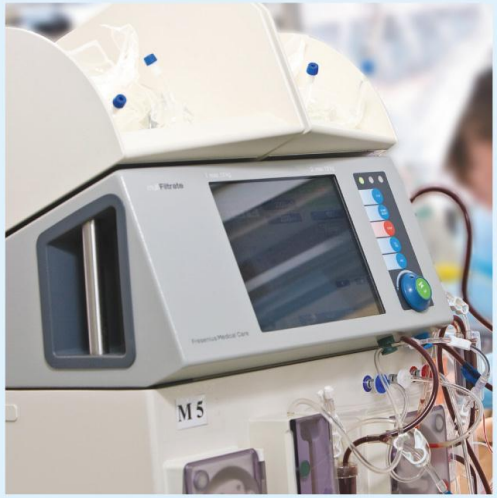


Současný stav poznatků o léčbě MM: co znamenají pro klinickou praxi? (Výstupy z klinických studií vs. klinická praxe)



Mikulov
2014

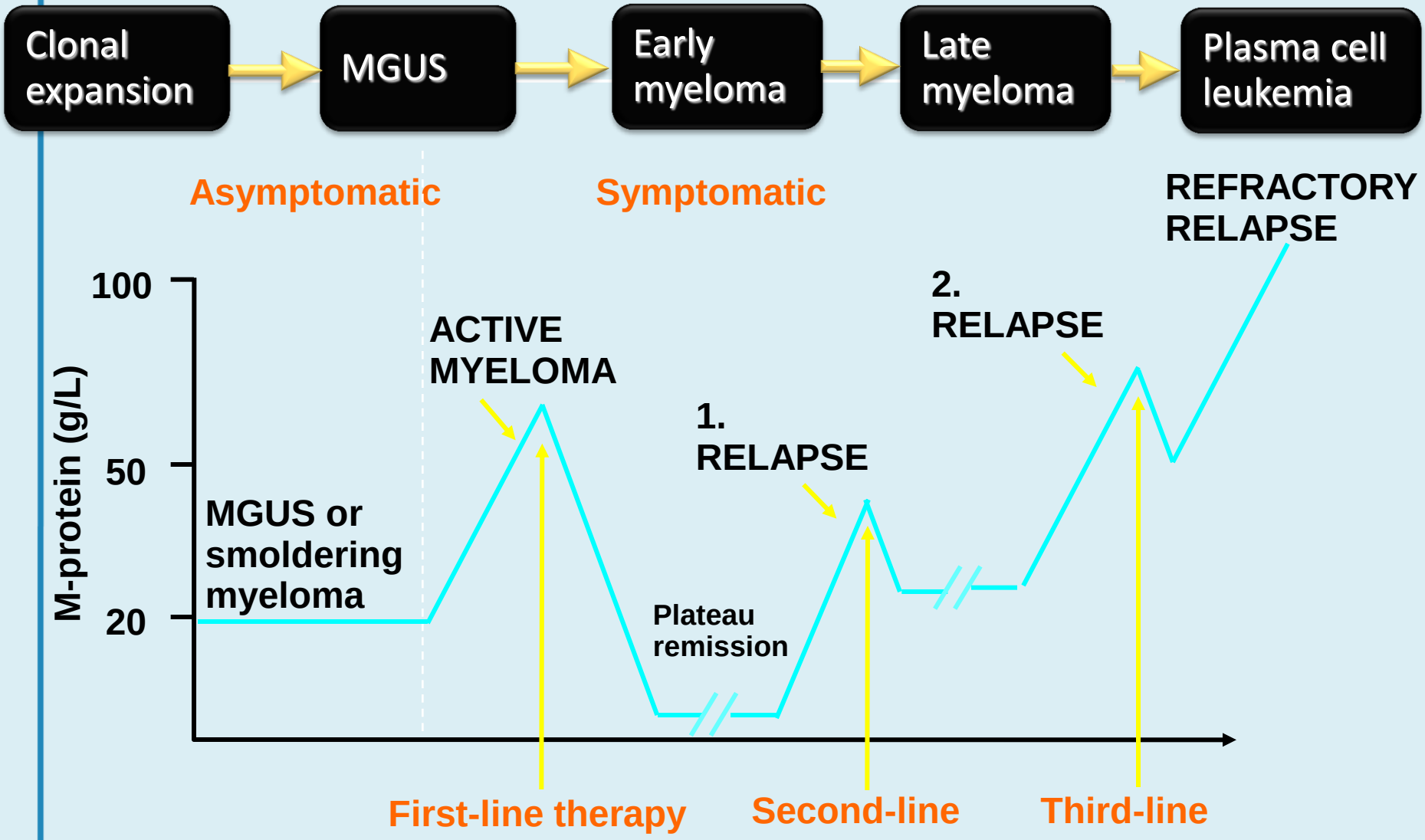
www.fno.cz

Tato prezentace vznikla za finanční podpory společnosti Janssen-Cilag s.r.o.

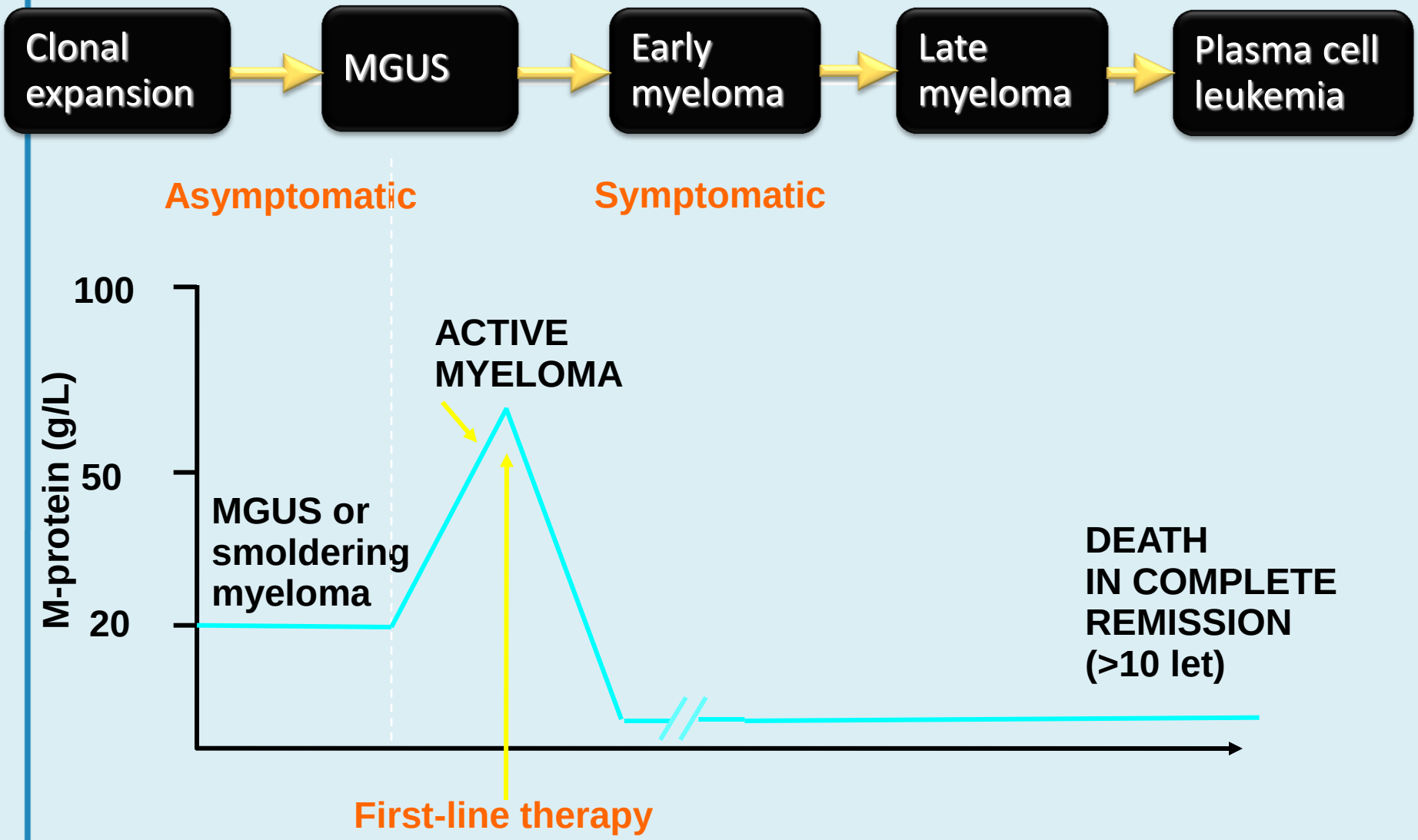
FAKULTNÍ NEMOCNICE OSTRAVA

Úvod

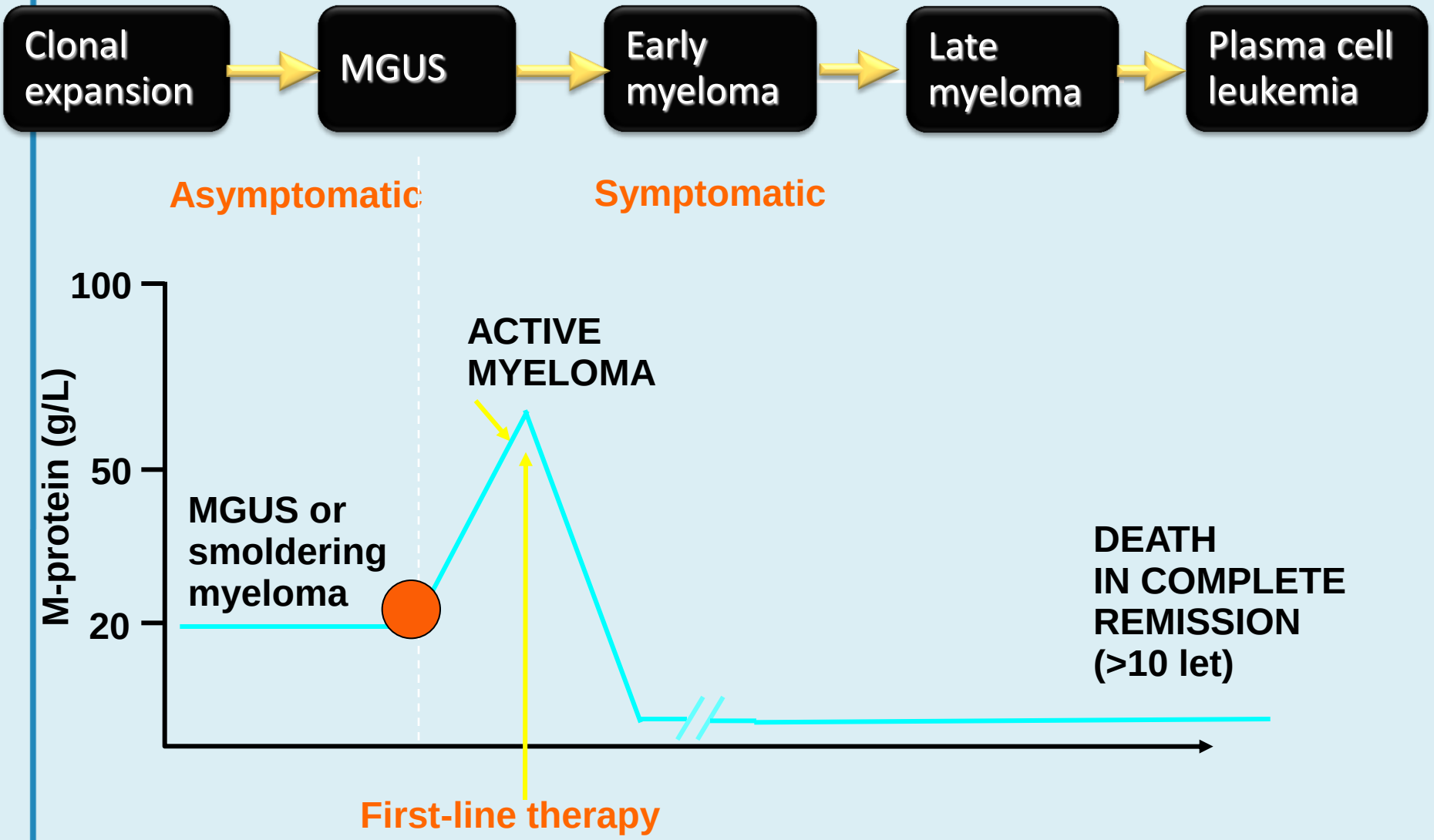
Natural history of multiple myeloma



Natural history of multiple myeloma



Natural history of multiple myeloma



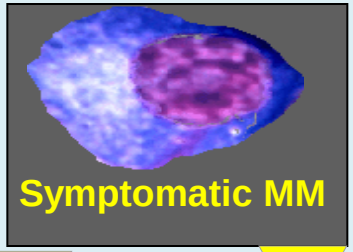
MM: Oncology perspective

Clonal expansion → MGUS → Early myeloma → Late myeloma → Plasma cell leukemia

MILESTONES:

1. ***Molecular or Immunophenotypic REMISSION***
2. ***Sustained REMISSION***

Intervention



Agressive clonal selection

Cure

Chronic disease management

Personalised medicine

&

„targeted“ treatment?

We need novel therapeutic strategies

~~Personalised medicine~~

~~&~~

~~„targeted“ treatment?~~

From diagnosis to treatment

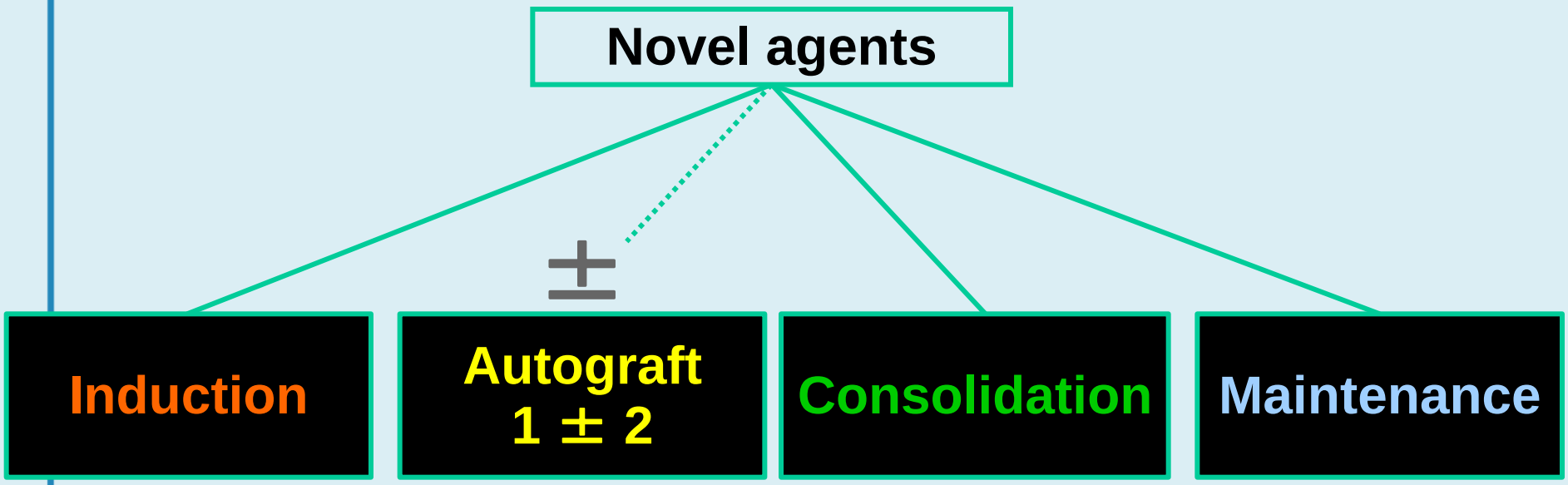
ALL (TWO) novel drugs

+

glucocorticoids and alkylating agents

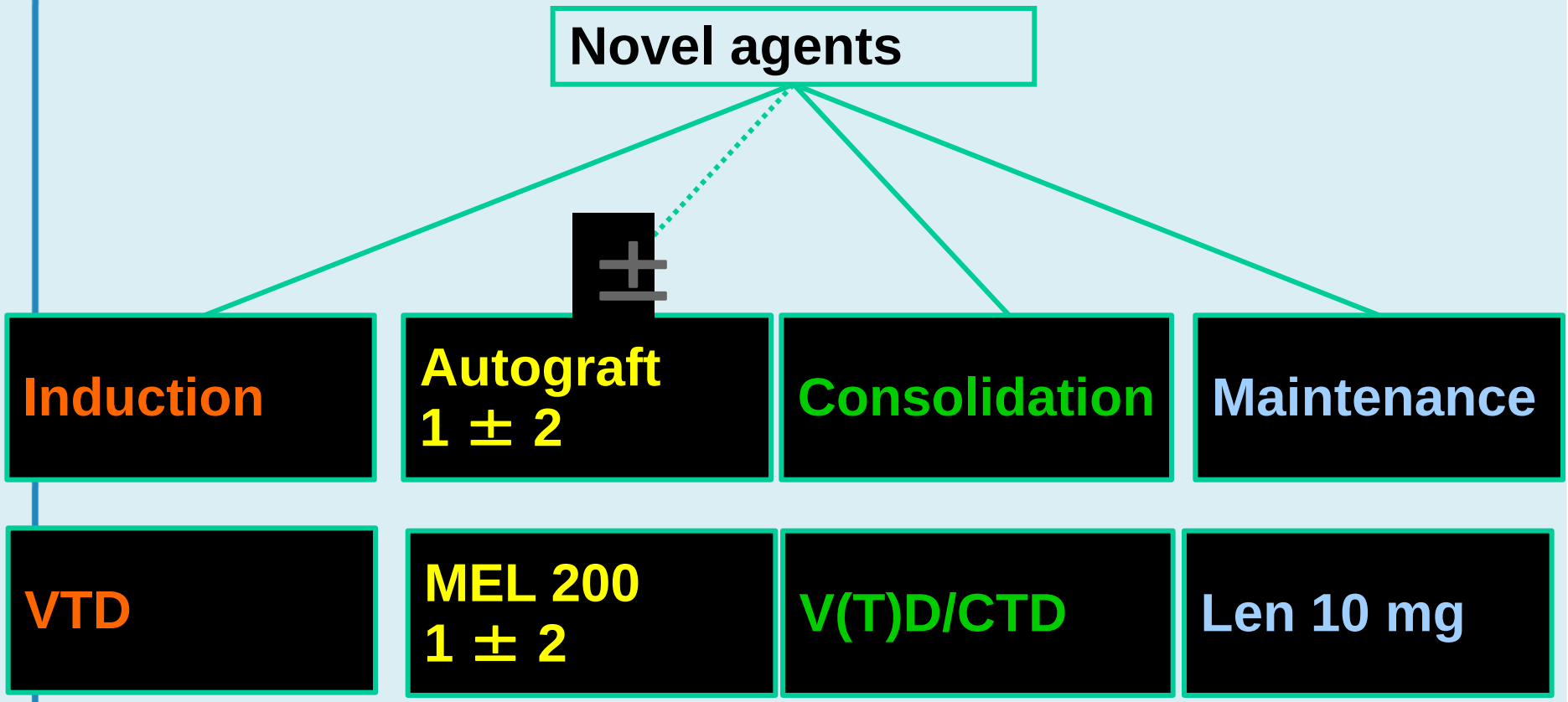
upfront

NEW treatment paradigm for newly diagnosed patients



Multi Agent Sequential Therapy Targeting Different Clones

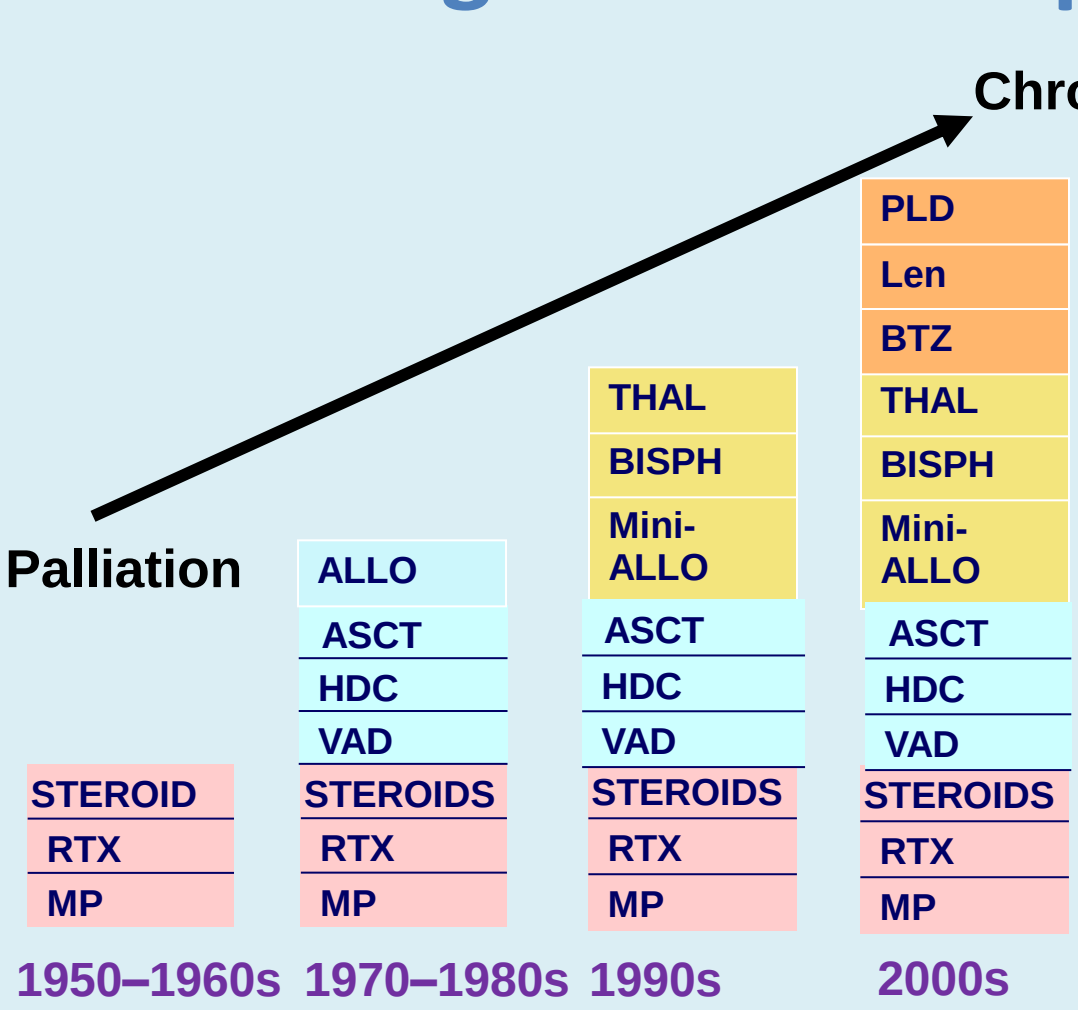
Recommendation in CMG guidelines for Czech Republic



Multi Agent Sequential Therapy Targeting Different Clones

Klíčové účinné léky u MM

MM: Progress in Therapeutic Options



2013

New Targets/Agents

Hsp90	KOS 953
Proteasome	PR171, NPI0052
Aggresome	Tubacin
HDAC	LBH, SAHA
Akt	elotuzumab
XBP-1	XBP-1 peptide
Muc-1	NM3
MEK	AZD6244
NF-kB	NPI1387
PKC	Enzastaurin
p38MAPK	SCIO469
Telomerase	GRN 163L
Natural products	EGCG
ARRY 520	daratumumab

- Develop effective combination with induction, and consolidation and maintenance strategy
- Genome-based selection
- Prevent progression

BTZ = Bortezomib
BISPH = Bisphosphonates
THAL = Thalidomide

ASCT = Stem cell transplantation
HDC = High-dose chemotherapy
MP = Melphalan + Prednisone

PLD = Pegylated liposomal doxorubicin

MM:Progress in Therapeutic Options
Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

MM:Progress in Therapeutic Options
Key effective drugs

Alkylating agens	melphalan cyclophosphamid bendamustin
Glucocorticoids	prednisolon dexamethason
IMIDs	thalidomide lenalidomide pomalidomide
Proteasome inhibitors	i.v. : bortezomib, carfilzomib, MLN, marizomib s.c.: bortezomib p.o.: MLN (ixazomib), oprozomib, delanzomib

MM: Progress in Therapeutic Options
Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

Přes obrovský vývoj nových molekul potenciálně účinných u MM patří a ještě delší dobu budou patřit tyto 3 (USA) 4 (EU) klíčové skupiny léků mezi „NEJ“ u MM

IMIDs and Proteasome inhibitors

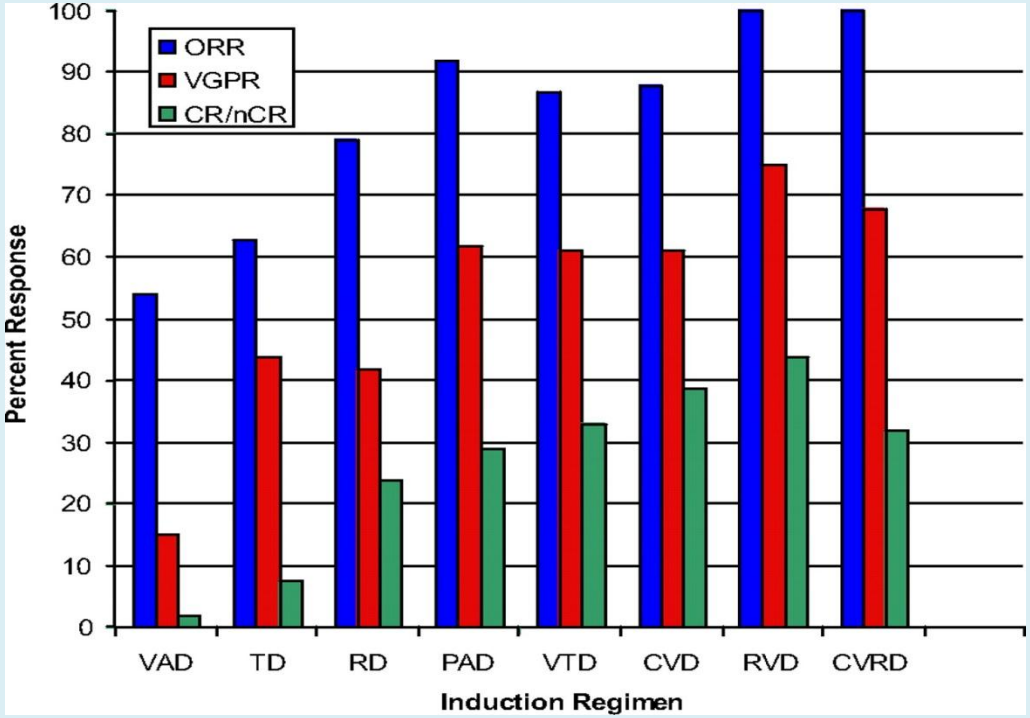
- Multiple mechanisms of action
- Strong anti-myeloma effect
- Non targeted drugs
- No predictors of sensitivity/resistance

1. Kupperman E, et al. Cancer Res 2010; 70(5): 1970-80
2. Chauhan D, et al. Clin Cancer Res 2011;17(16):5311–21
3. Lee EC, et al. Clin Cancer Res 2011; 17(23): 7313-23
4. Chattopadhyay N et al. AACR 2011, Orlando, FL, USA (Abstract 2828)

Možnosti stávající léčby

MM: Progress in Therapeutic Options
Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors



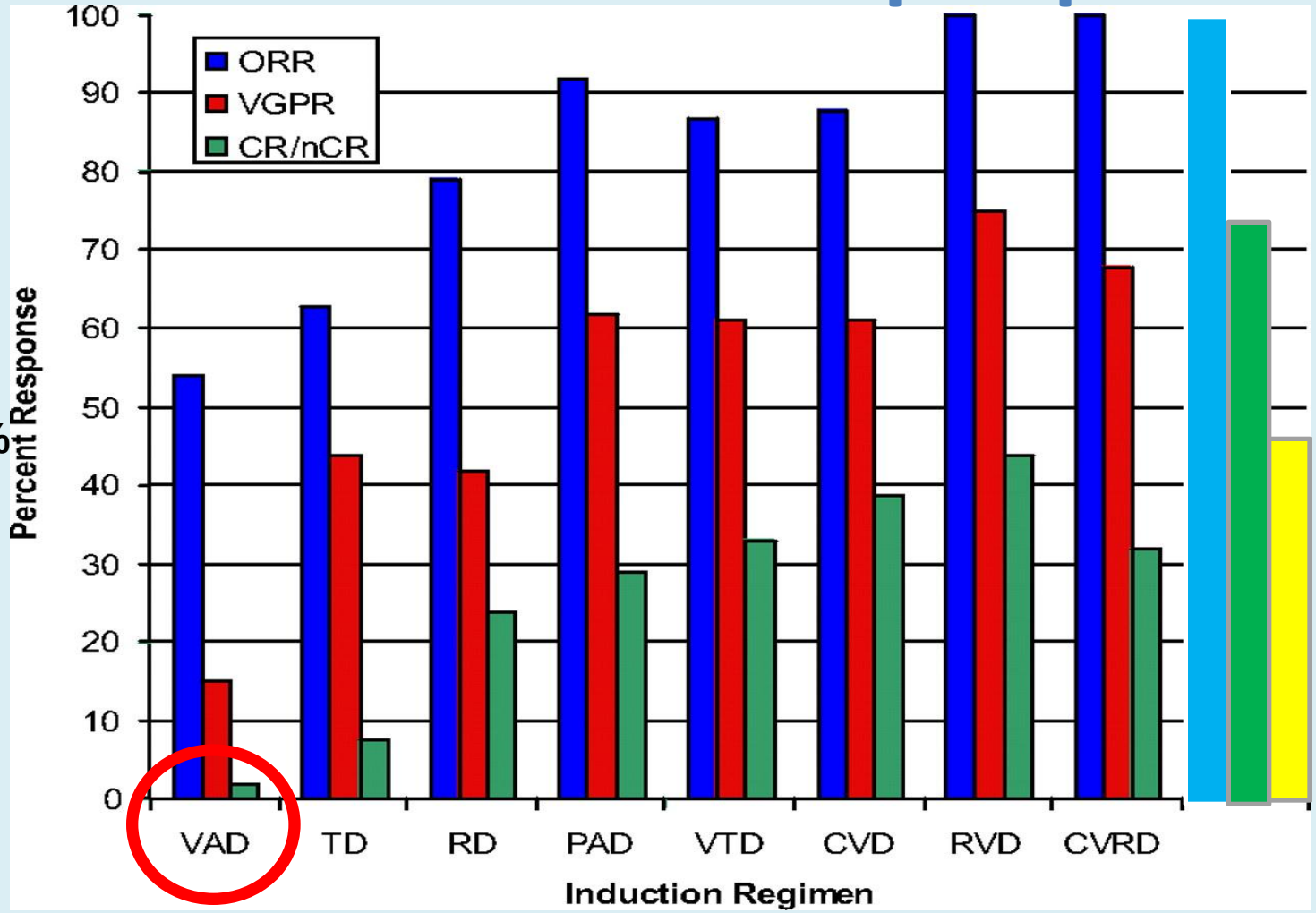
MODIFIED, Stewart AK, et al. Blood. 2009;114:5436-43.

Combinations in the upfront treatment of MM – near perspective

50-60% ORR

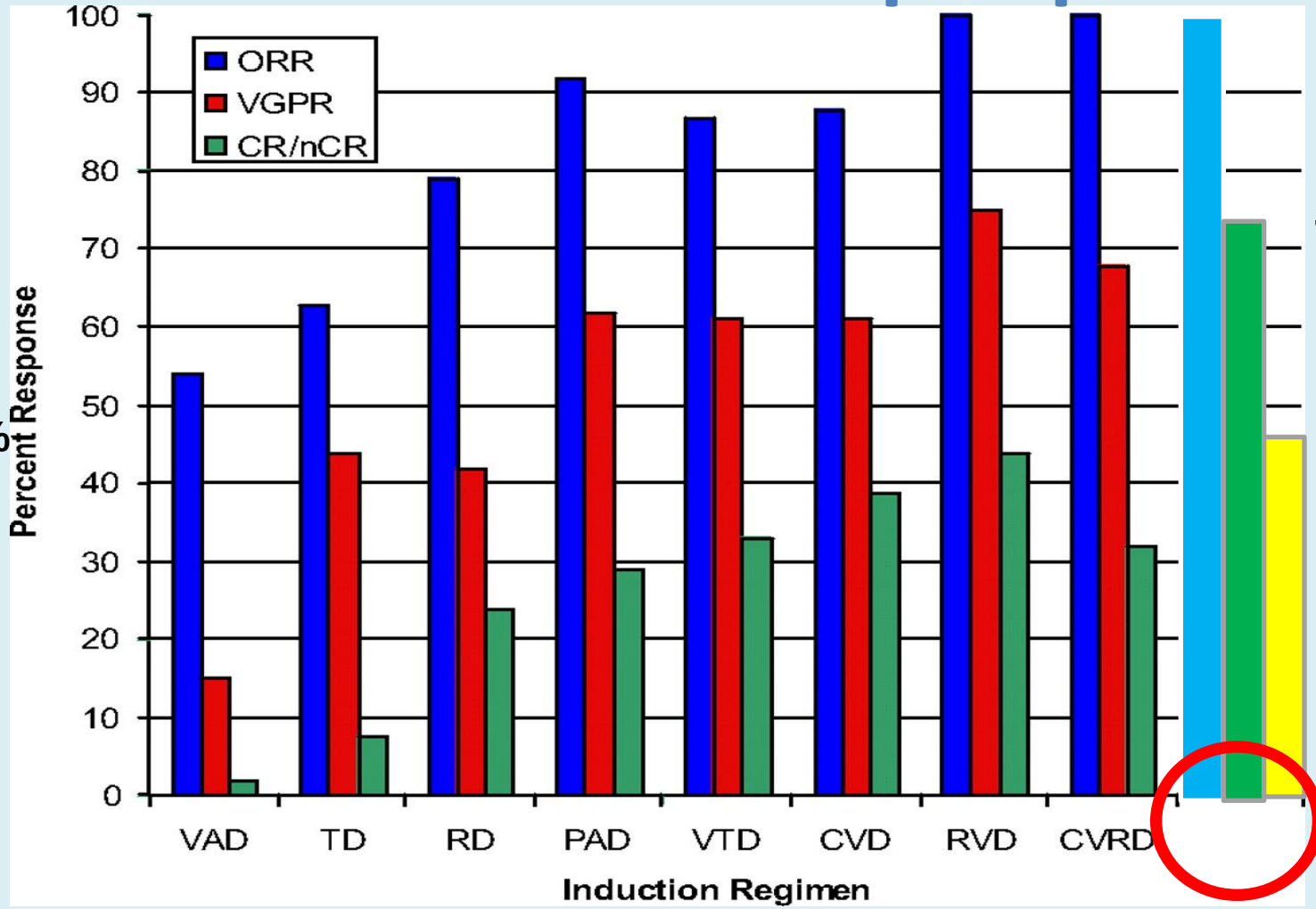
< 5% CR

? % i/mCR?



MODIFIED, Stewart AK, et al. Blood. 2009;114:5436-43.

Combinations in the upfront treatment of MM – near perspective



50-60% ORR

< 5% CR

? % i/mCR?

100% ORR

70-80% CR

30-40% i/mCR?

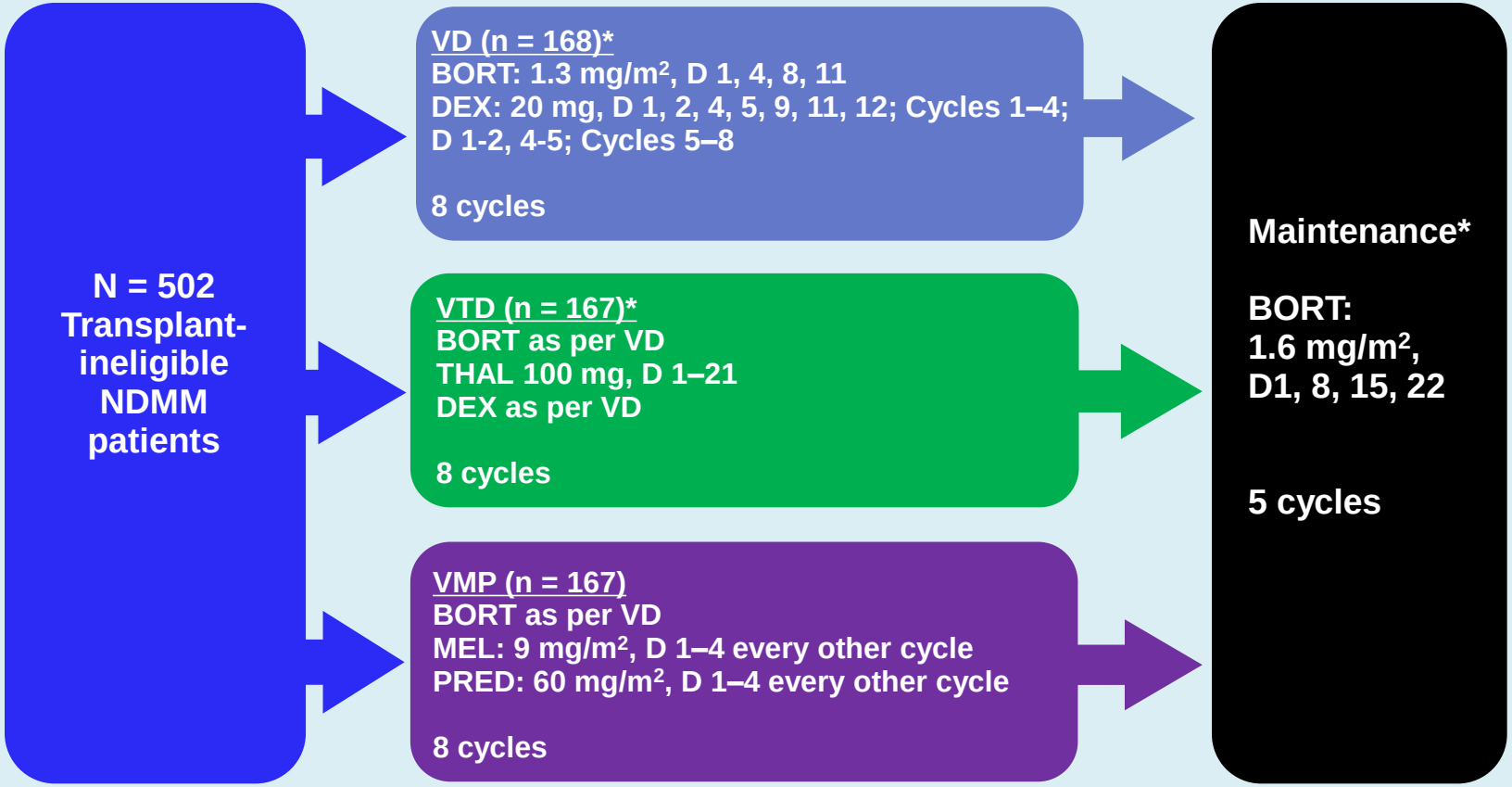
MODIFIED, Stewart AK, et al. Blood. 2009;114:5436-43.

MM

-

Kombinace IMIDs a PIs

Bortezomib Combinations as Induction Therapy for Elderly NDMM Patients (Phase 3 UPFRONT Trial): *Final analysis*



- Primary end-point: PFS, secondary end-points: ORR, OS, TTNT

**Jediným aktuálně schváleným režimem s bor v primoléčbě u netransplantabilních pacientů je režim VMP (dle SPC Velcade v01/2014).*

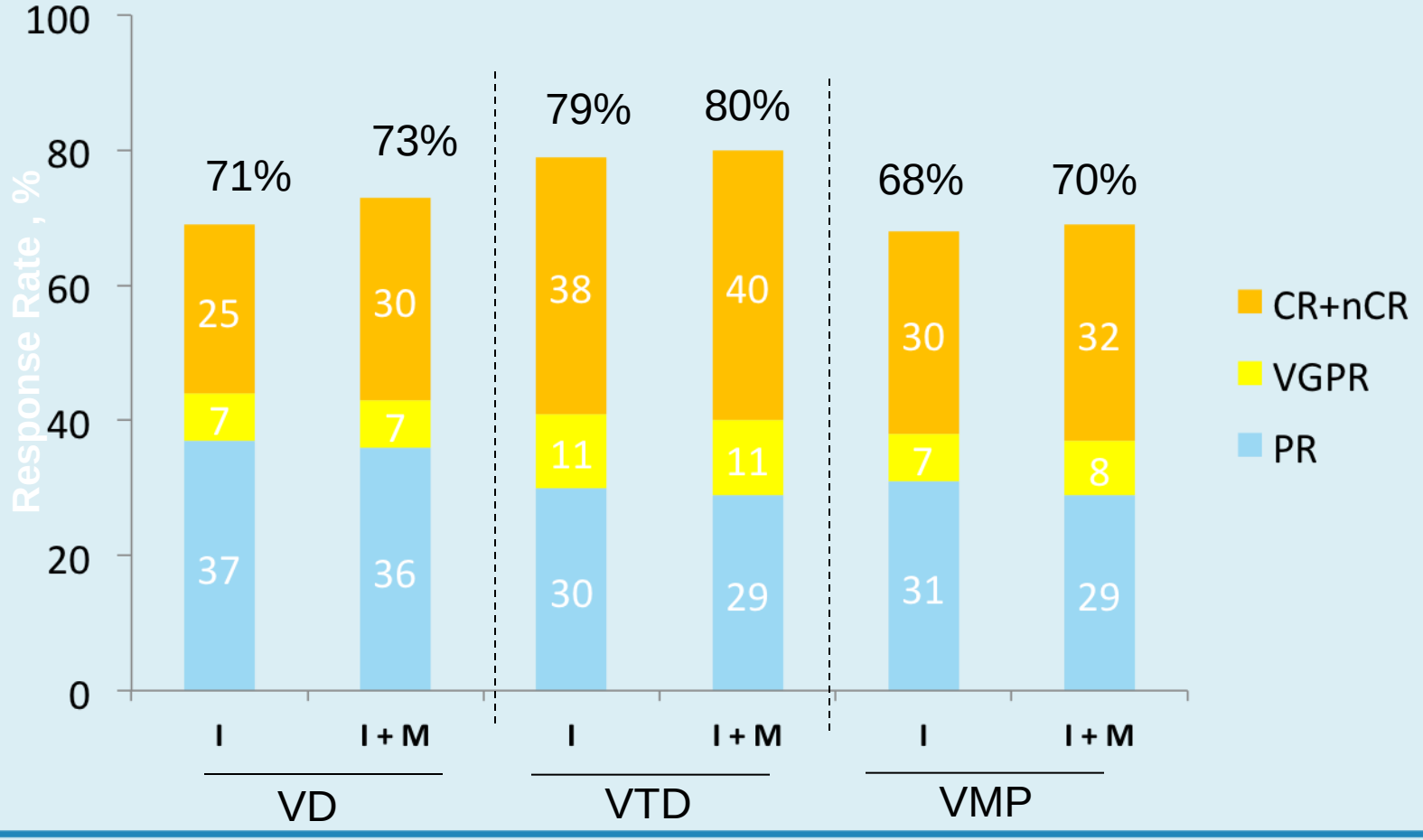
VD, bortezomib, dexamethasone; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone

Niesvizky R, et al. *Blood*. 2013;122:abstract 1966. Updated data presented at ASH 2013.

FAKULTNÍ NEMOCNICE OSTRAVA

Phase 3 UPFRONT Trial – VD vs VTD vs VMP: Response Rates

- ≥ VGPR rates were higher in VTD compared to VD (p = 0.0153)



I, induction; M, maintenance;
VD, bortezomib, dexamethasone;
VMP, bortezomib, melphalan, prednisone;
VTD, bortezomib, thalidomide, dexamethasone

Niesvizky R, et al. *Blood*. 2013;122:abstract 1966.
Updated data presented at ASH 2013.

FAKULTNÍ NEMOCNICE OSTRAVA

Nestačí zvláště u fragilních a starších nemocných jen IMID nebo PI s dexametazonem?

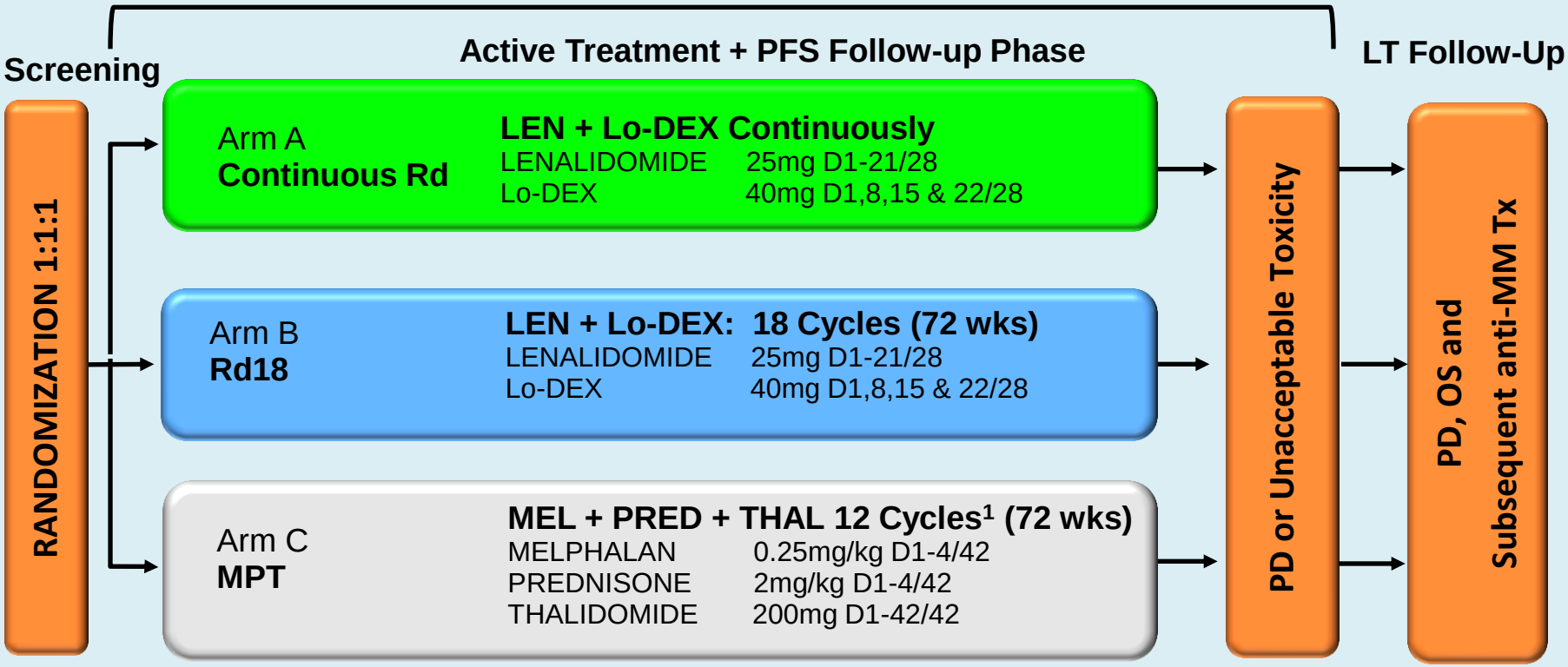
Abstract 2

Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701

- Thierry Facon, Meletios A. Dimopoulos, Angela Dispenzieri, John V. Catalano, Andrew R. Belch, Cyrille Hulin, Michele Cavo, Antonello Pinto, Katja Weisel, Heinz Ludwig, Nizar J. Bahlis, Anne Banos, Mourad Tiab, Michel Delforge, James D. Cavenagh, Catarina Geraldes, Je-Jung Lee, Christine I. Chen, Albert Oriol, Javier De La Rubia, Lugui Qiu, Darrell J. White, Daniel Binder, Kenneth C. Anderson, Philippe Moreau, Michel Attal, Robert Knight, Guang Chen, Jason Van Oostendorp, Christian J. Jacques, Annette Ervin-Haynes, Lotfi Benboubker

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

FIRST Trial: Study Design



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

- Stratification: age, country and ISS stage

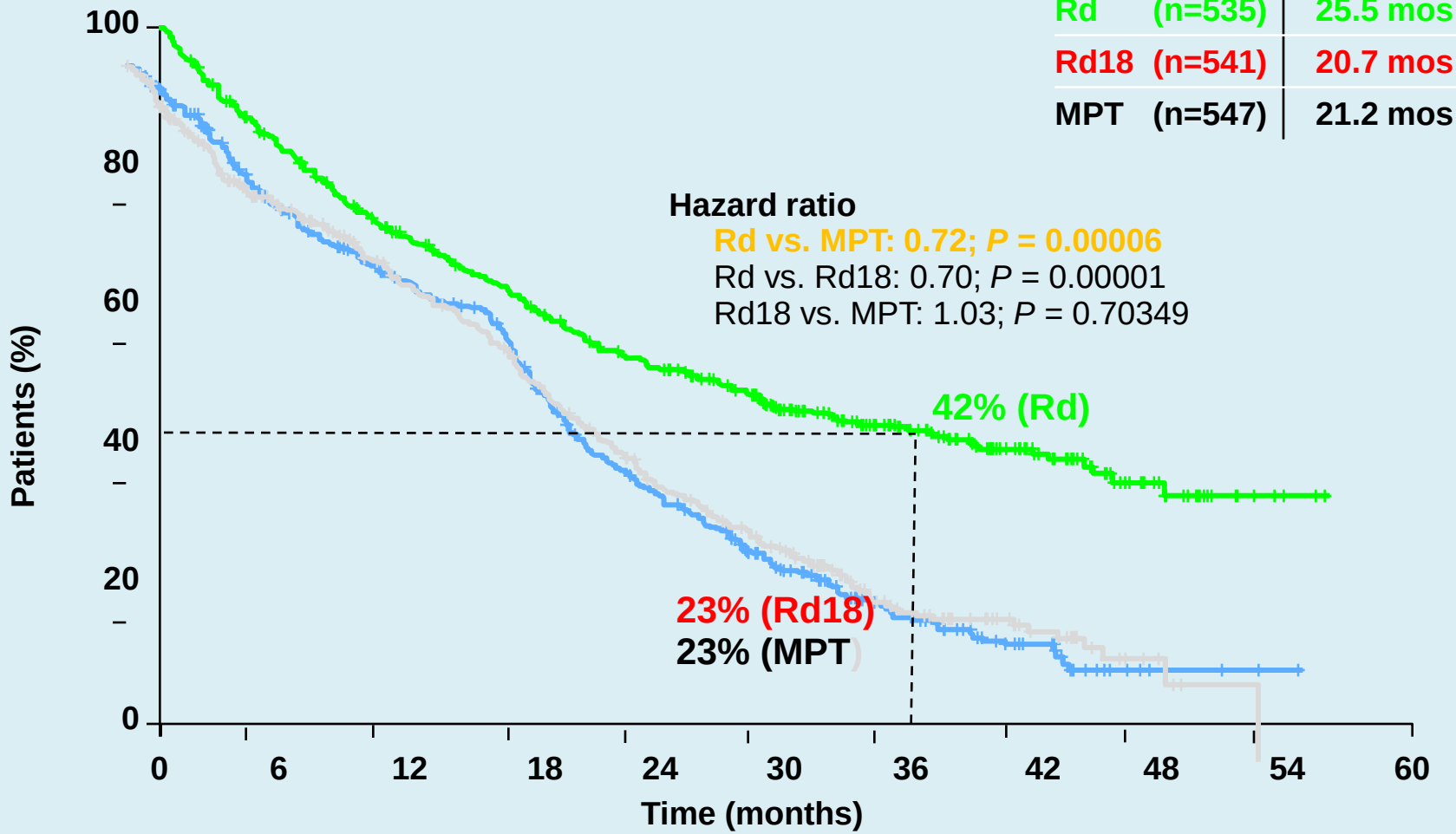
ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

[1]Facon T, et al. Lancet 2007;370:1209-18; [2]Hulin C, et al. JCO. 2009;27:3664-70.

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

FIRST Trial: Final Progression-free Survival

		Median PFS
Rd	(n=535)	25.5 mos
Rd18	(n=541)	20.7 mos
MPT	(n=547)	21.2 mos



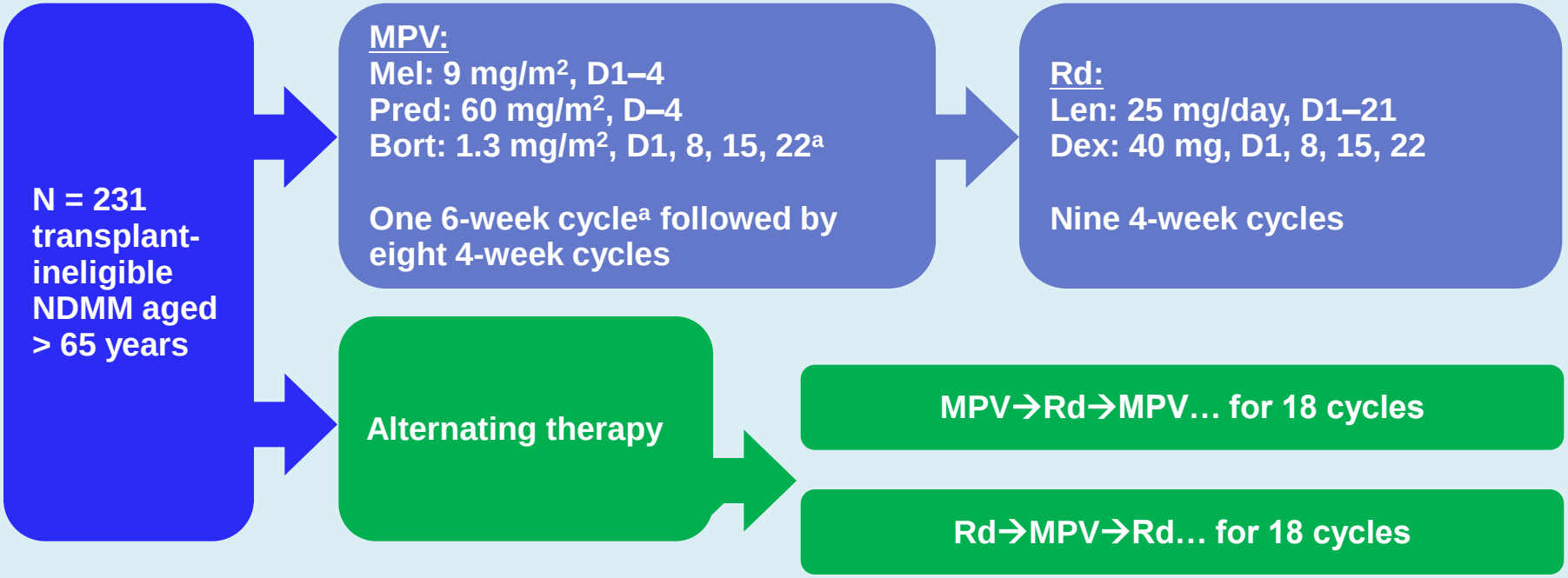
Rd	535	400	319	265	218	168	105	55	19	2	0
Rd18	541	391	319	265	167	108	56	30	7	2	0
MPT	547	380	304	244	170	116	58	28	6	1	0

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

Nové přístupy

Sequential vs Alternating VMP and Rd in NDMM

- **Randomized phase 2 study to** compare the efficacy and safety of two treatment schemes (MPV followed by Rd or MPV alternating with Rd)



- Primary end-points: TTP, safety; secondary end-points: RR, DOR, OS
- Subanalysis in patients with high-risk cytogenetics

[a] During the first cycle (6 weeks), bortezomib is given on D1, 4, 8, 11, 22, 25, 29, and 32.

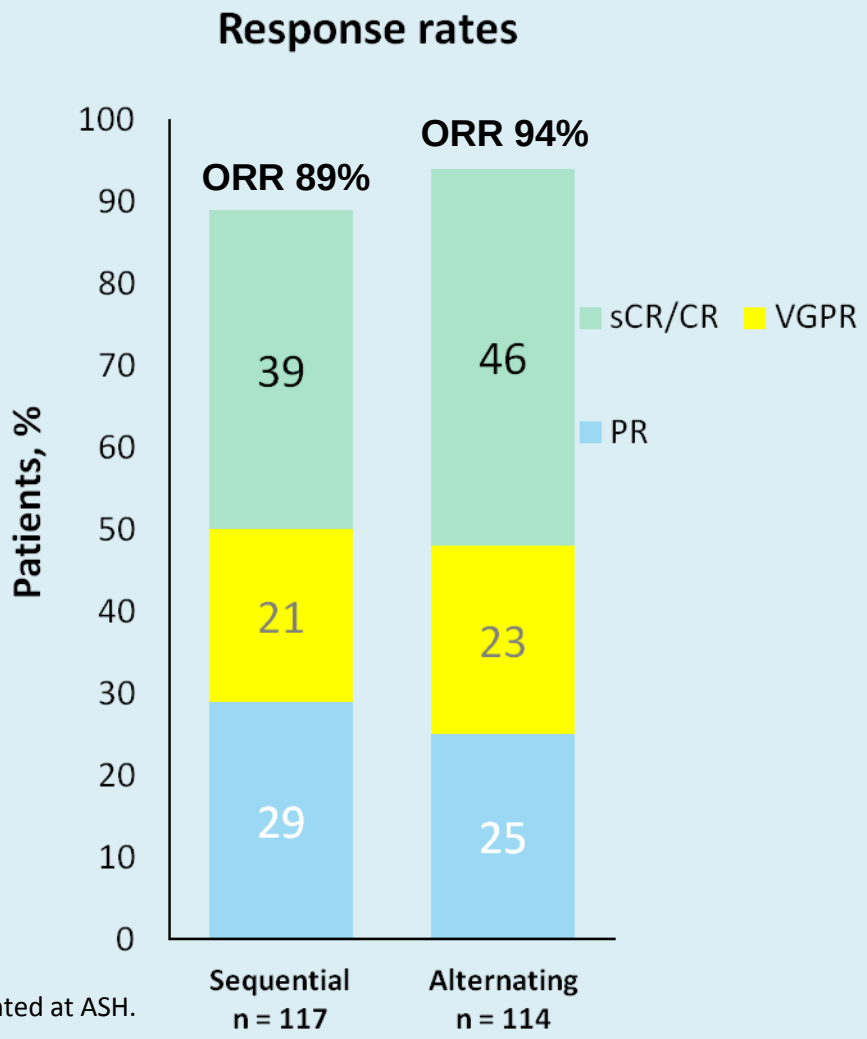
Mateos MV, et al. *Blood*. 2013;122:abstract 403. Updated data presented at ASH.

Sequential vs Alternating VMP and Rd: Response

- Median number of 13 cycles (1-18)

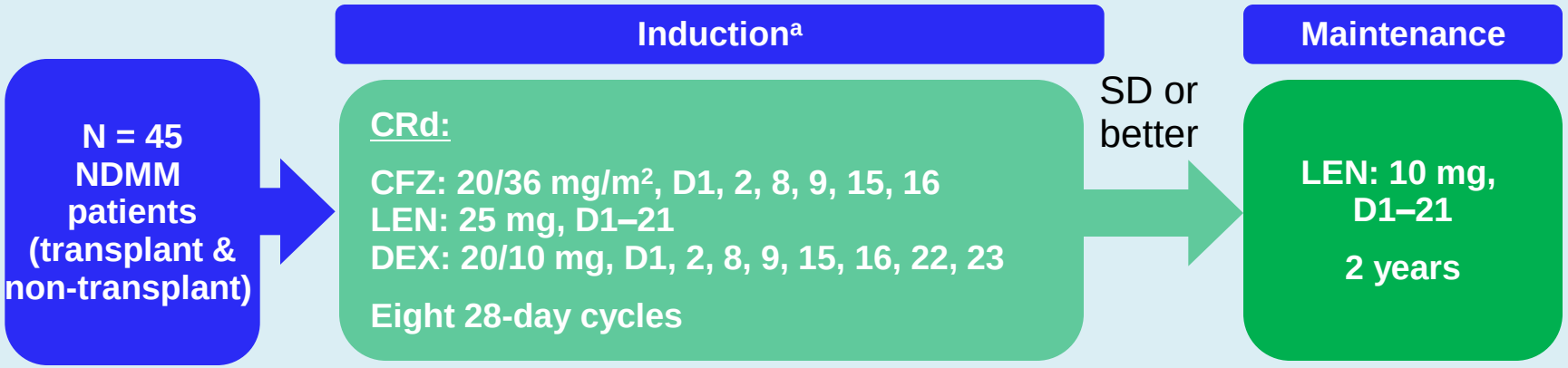
Subanalysis:

- CR rates were similar across different subgroups for both arms, including
  - pts aged < vs ≥ 75 yrs
  - ISS stage I/II vs III
  - cytogenetic abnormalities



Mateos MV, et al. *Blood*. 2013;122:abstract 403. Updated data presented at ASH.

CRd (Carfilzomib, Lenalidomide, Low-Dose Dex) Followed by Lenalidomide Extended Dosing (CRd-R)



- 45 patients enrolled (median age 60 years, range 40–88)
- Median of 12 cycles of CRd-R received
- Primary objective was to determine the incidence of ≥ grade 3 neuropathy, secondary objectives included correlatives (GEP, biomarkers, proteasomes, flow cytometry, PCR, etc.) and ORR, PFS, OS, DoR

[a] Patients < 75 years underwent stem cell collection after cycle 4, then continued therapy.

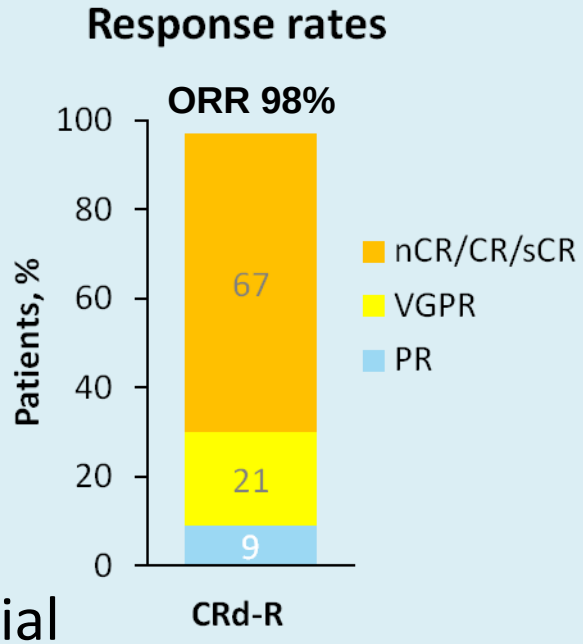
CRd, carfilzomib, Lenalidomide, low-dose dexamethasone

Korde N, et al. *Blood* 2013;122: abstract 653. Updated data presented at ASH 2013.

CRd Followed by Lenalidomide Extended Dosing (CRd-R): Efficacy and Safety

Efficacy

- ORR was 98%, with 88% ≥VGPR (n = 43)
- Median time to reach CR/sCR was 5 months
- Response rates based on FISH/cytogenetics or age (65 years cut-off) were non-differential
- PFS at 18 months was 91%; of 27 nCR/CR patients assessed
- by flow cytometry, all are MRD negative



CRd, carfilzomib, lenalidomide, low-dose dexamethasone; LFT, liver function test

Korde N, et al. *Blood* 2013;122: abstract 653. Updated data presented at ASH 2013.

Závěr

MM:Progress in Therapeutic Options
Key effective drugs

Alkylating agens	melphalan cyclophosphamid bendamustin
Glucocorticoids	prednisolon dexamethason
IMIDs	thalidomide lenalidomide pomalidomide
Proteasome inhibitors	i.v. : bortezomib, carfilzomib, MLN, marizomib s.c.: bortezomib p.o.: MLN (ixazomib), oprozomib, delanzomib

MM: Future in Therapeutic Option

IMIDs and PI combo regimens

100% - ORR; 1/3 of mCR/iCR

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

MM: Futurein Therapeutic Option

IMIDs and PI combo regimens for several treatment lines

Glucocorticoids **thalidomid** **bortezomib** VTD

MM: Future in Therapeutic Option

IMIDs and PI combo regimens for several treatment lines

Glucocorticoids	thalidomid	bortezomib	VTD
Glucocorticoids	lenalidomide	carfilzomib	CRD

MM: Future in Therapeutic Option
IMIDs and PI combo regimens for several treatment lines

Glucocorticoids	thalidomid	bortezomib	VTD
Glucocorticoids	lenalidomide	carfilzomib	CRD
Glucocorticoids	pomalidomide	ixazomib	IPD

MM: Future in Therapeutic Option
IMIDs and PI combo regimens for several treatment lines

Glucocorticoids	thalidomid	bortezomib	VTD
Glucocorticoids	lenalidomide	carfilzomib	CRD
Glucocorticoids	pomalidomide	ixazomib	IPD
Glucocorticoids	pomalidomide	oprozomib	OPD

Combinations of IMIDs and PIs with Glucocorticoids are the most effective regimens

There is not cross resistance thus rotation of different members from IMIDs and PIs is possible in RRMM

Moreover some of regimens are fully „per os“ regimen

Glucocorticoids	pomalidomide	ixazomib	IPD
Glucocorticoids	pomalidomide	oprozomib	OPD

VTD

CRD

MM: Progress in Therapeutic Options
Key effective drugs

- Alkylating agens
- Glucocorticoids
- IMIDs
- Proteasome inhibitors

Despite many novel agens evaluation in the clinical trials phase I/II

IMIDs and PIs

remain key players & backbone of myeloma treatment on NDMM, as well as RRMM for this decade

Acknowledgement

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Thank you for your attention.